PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)

(PCT Rule 44bis I(c))

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MAY 1.6 2011

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IMPORTANT NOTICE

International application No. PCT/US2008/080370 International filing date (day/month/year)
17 October 2008 (17.10.2008)

Priority date (day/month/year)

Applicant

JANSSEN ALZHEIMER IMMUNOTHERAPY et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)



The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

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Form PCT/IB/326 (January 2004)

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PATENT COOPERATION TREATY

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

	(PCT Rule 44bis)	
Applicant's or agent's file reference 15270C-19-11	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2008/080370	International filing date (day/month/year) 17 October 2008 (17.10.2008)	Priority date (day/month/year)
International Patent Classification (8) See relevant information in Form	h edition unless older edition indicated) PCT/ISA/237	
Applicant JANSSEN ALZHEIMER IMMUNC	THERAPY	

. :	This international preliminar International Searching Authority	y report on patentability (Chapter I) is issued by the International Burority under Rule $44\ bis.1(a)$.	can on behalf of the
;	This REPORT consists of a	total of 9 sheets, including this cover sheet.	
	In the attached sheets, any re- reference to the international	eference to the written opinion of the International Searching Authorit preliminary report on patentability (Chapter I) instead.	ty should be read as a
:	This report contains indication	ons relating to the following items:	
	Box No. I	Basis of the report	
	Box No. II	Priority	
	Box No. III	Non-establishment of opinion with regard to novelty, inventive applicability	step and industrial
	Box No. IV	Lack of unity of invention	
	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, industrial applicability, citations and explanations supporting su	
	Box No. VI	Certain documents cited	
	Box No. VII	Certain defects in the international application	
	Box No. VIII	Certain observations on the international application	
	The International Bureau will but not, except where the ap the priority date (Rule 44bis	I communicate this report to designated Offices in accordance with R plicant makes an express request under Article 23(2), before the expi. (2).	tules 44bis 3(c) and 93bis 1 ration of 30 months from

	Date of issuance of this report 19 April 2011 (19.04.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou
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Form PCT/IB/373 (January 2004).

PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY ROSEMARIE L. CELLI TOWNSEND AND TOWNSEND AND CREW LLP WRITTEN OPINION OF THE TWO EMBARCADERO CENTER INTERNATIONAL SEARCHING AUTHORITY 8TH FLOOR SAN FRANCISCO, CA 94111-3834 (PCT Rule 43bis.1) Date of mailing 22 JAN 2009 (day/month/year) Applicant's or agent's file reference FOR FURTHER ACTION 15270C-19-11 See paragraph 2 below International application No. International filing date (day/month/year) Priority date (day/month/year) PCT/US 08/80370 17 October 2008 (17,10,2008) 17 October 2008 (17.10.2008) International Patent Classification (IPC) or both national classification and IPC IPC(8) - A61K 38/00 (2008.04) USPC - 514/2 Applicant ELAN PHARMA INTERNATIONAL LIMITED 1. This opinion contains indications relating to the following items: Box No. 1 Basis of the opinion Box No. II Priority Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Box No. IV Lack of unity of invention Reasoned statement under Rule 43bis. I(a)(i) with regard to novelty, inventive step or industrial applicability; Box No. V citations and explanations supporting such statement Box No. VI Certain documents cited Box No. VII Certain defects in the international application Box No. VIII Certain observations on the international application 2. FURTHER ACTION If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered. If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. For further options, see Form PCT/ISA/220. For further details, see notes to Form PCT/ISA/220. Name and mailing address of the ISA/US Date of completion of this opinion Authorized officer: Mail Stop PCT, Attn: ISA/US Les W. Young Commissioner for Patents 22 December 2008 (22.12.2008) P.O. Box 1450, Alexandria, Virginia 22313-1450 PCT Helpdask: 571-272-4300

Form PCT/ISA/237 (cover sheet) (April 2007)

Facsimile No. 571-273-3201

International application No.

PCT/US 08/80370

	No.1	Basis of this opinion	<u> </u>	<u> </u>	n nest term		
1.	With s	egard to the language, this c	opinion has been establ	ished on the basis	of:		
	区	the international application	n in the language in wi	nich it was filed.			
}		a translation of the internal translation furnished for th		onal search (Rules	which 12.3(a) and 23.1(b))	is the langu	uage of a
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2.		This opinion has been estal to this Authority under Ru	olished taking into acco te 91 (Rule 43 <i>bis</i> , I(a))	unt the rectificatio	n of an obvious mistal	ke authorized by	or notified
3.		egard to any nucleotide and shed on the basis of:	d/or smino scid sequ	ence disclosed in ti	ne international applica	tion, this opinic	on has been
		e of material		र व			
		a sequence listing				a ^r	
		able(s) related to the s	equence listing				
	b. for	mat of material					
	- 1	on paper in electronic form					-
	<u> </u>	T m elecanule torm					
4,		e of filing/furnishing contained in the intern filed together with the furnished subsequently	international application to this Authority for the	n in electronic fon			
1		In addition, in the case that filed or furnished, the requ in the application as filed of	ired statements that the	information in the	subsequent or addition	al copies is iden	
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5.	Additi	filed or furnished, the requ	ired statements that the	information in the	subsequent or addition	al copies is iden	
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International application No.

PCT/US 08/80370

Box No.	III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
The ques	tions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially the have not been examined in respect of
	the entire international application
NZI	Claims Nos
*	Cash D 1903.
becau	se:
	the said international application, or the said claims Nos
	subject matter which does not require an international search (specify):
M	the description, claims or drawings (indicate particular elements below) or said claims Nos. 8, 10-17, 36-40, 104-115
**************************************	are so unclear that no meaningful opinion could be formed (specify):
second a	10-17, 36-40, 104-115 are unsearchable because they are dependent claims and are not drafted in accordance with the of third sentences of Rule 8.4(a). Note: claim 8 fails to claim multiple dependency in the alternative.
	the claims, or said claims Nos. are so inadequately supported
	by the description that no meaningful opinion could be formed (specify):
	· · · · · · · · · · · · · · · · · · ·
1521	8, 10-17, 36-40, 104-115
8228	no international search report has been established for said claims Nos.
	a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
	furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable
	to it.
	furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable
	pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under
	Rule 13ter. 1(a) or (b).
	a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
	the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
	See Supplemental Box for further details.

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1.	Statement			
	Novelty (N)	Claims	3-4, 9, 18-35, 41-56, 60, 74-75, 95-103	YES
	morely feet	Claims	1-2, 5-7, 57-59, 61-73, 76-94	_ NO
			None	
	Inventive step (IS)	Claims	1-7, 9, 18-35, 41-103	_ YES
		Claims		NO
	Industrial applicability (IA)	Claims	1-7, 9, 18-35, 41-103	YES
		Claims	None	NO
				· · · · · · · · · · · · · · · · · · ·
•	Citations and explanations:			
im	s 1-2, 5-7, 57-59, 61-73, and 76-94	lack novelty u	nder PCT Article 33(2) as being anticipated by US 2006/0193850 A1 t	o Warne
(t)e	reinafter "Warne").			15 46 50 1
	alaine 4. Manas tanahan a madhad a	o observaciones o	illy treating Alzheimer's disease (para (0036), (0050)), comprising admi	
			sty treating Atznelmer's disease (para [0030], [0030]), comprising admit ase (para [0036], [0098]) a dosage of an antibody within a range of ab	
eller Serv	to less than 5 mg/kg (para 100351)	wherein the a	and (para (outo), (outo)) a codage to an arracco mains a large or ab- antibody specifically binds to beta amyloid peptide (A-beta) with a bindi	ບບເ ບ.ບ ກດ ຂາຍຄນ
	st 10e7 M-1 (para [0059)), and there			
	The state of the s	a de la responsación de la compansación de la compa	en de la companya de En la companya de la	
			lly treating Alzheimer's disease (para (0036), (0050)), comprising admi	
RY	enaus infusion to a astient sufferina	from the dise:	ase (para [0036], [0098]) a dosage of an antibody within a range of ab	out 0.5
2		4 4 4		
	to less than 5 mg/kg (para (0035)),		entibody specifically binds to an N-terminal fragment of beta amyloid or	
	to less than 5 mg/kg (para (0035)),		antibody specifically binds to an N-terminal fragment of beta amyloid po 0059], [0127]), and thereby therapeutically treat the patient (para [0036	
ita)	to less than 5 mg/kg (para (0035]), with a binding affinity of at least 10e	7 M-1 (para (0	0059], [0127]), and thereby therapeutically treat the patient (pará [0036	S)).
sta) s to	to tess than 5 mg/kg (para [0035]), with a binding affinity of at least 10e claims 5-7. Warne teaches that the	7 M-1 (para (0 antibody is a t	0059], [0127]), and thereby therapeutically treat the patient (para [0036 humanized version of mouse antibody 3D6 expressed by the hybridon	ij). sa deposi
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Supplemental Sox

in case the space in any of the preceding boxes is not sufficient. Continuation of:

Box V.2. Citations and Explanations:

As to claim 67-94. Warns teaches a method of treating Alzheimer's disease (para [0036], [0050]), comprising: subcutaneously administering to a patient having the disease (para [0035]-[0036]) an entibody that specifically binds to an N-terminal fragment of A-beta (para [0127]), wherein the antibody is administered at a dose of 1-40 mg, 5-25 mg, 2.5-15 mg, 1-12 mg, 2.5-10 mg, 2.5-5 mg, 4-5 mg, or 7-10 mg (para [0174], [0176]) and a frequency of between weekly and monthly or weekly-biweekly (para [0172]-[0173]).

Claims 60, 74-75, and 95-103 lack an inventive step under PCT Article 33(3) as being obvious over Warne.

As to claim 60, Wame teaches a method of treating Atzheimer's disease (see explanation above for claim 57). Wame does not teach that the average serum concentration of is within a range of 2-4 ug antibody/ml serum. However, Warne teaches that the serum concentration is 1-1000 ug/ml (para [0173]), and it would have been obvious to one of skill in the art that the preferred serum concentration could fall anywhere in that range, including between 2-4 ug/ml.

As to claims 74-75. Warne does not teach that the average serum concentration of the entibody is maintained for at least six months or at least one year. However, it would have been obvious to one of skill in the art to maintain the average serum concentration of the antibody for such extended periods of time, because it would have been necessary to treat a chronic, progressive disease such as Alzheimer's disease.

As to claims 95-103, Warne teaches a method of treating Atzheimer's disease (para (0036), (0050)), comprising: administering to a patient having the disease (para (0036)) an antibody that specifically binds to an N-terminal fragment of A-beta (para (0127)) in a regime sufficient to maintain a serum concentration of the entibody in the patient of 1-1000 ug antibody/ml serum (para (0173)) and thereby treating the patient (para (0036)). Warne does not expressly teach that the maximum or average serum concentration of antibody is tess than about 28 ug/ml, within a range of about 4-28 ug/ml, 4-18 ug/ml, below about 7 ug/ml, within a range of 2-7 ug/ml, or about 5 ug/ml. However, it would have been obvious to one of skill in the art that the preferred serum concentration could fall anywhere in the disclosed range of 1-1000 ug/ml, including any of the recited ranges.

Claim 9 lacks an inventive step under PCT Article 33(3) as being obvious over Warne in view of US 2007/0082367 A1 to Godavarti et al. (hereinafter "Godavarti").

As to claim 9, Warne teaches a method of therapeutically treating Alzheimer's disease, wherein the antibody is a humanized antibody (see explanation above for claim 5). Warne further teaches that the humanized antibody is a humanized version of mouse antibody 12A11 (para (0010)). Warne does not teach that the antibody is expressed by the hybridoma deposited under ATCC under PTA-7271. Godavarti teaches a hybridoma expressing a humanized version of mouse antibody 12A11 deposited under ATCC under PTA-7271 (para (0137)-(0138)). It would have been obvious to one of skill in the art to use an antibody expressed by they hybridoma PTA-7271, because it would have been obvious to use a humanized 12A11 antibody from any known source.

Claims 18-20 and 23-28 lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of US 2006/0121038 A9 to Schenk et al. (hereinafter "Schenk").

As to claims 18 and 23, Warne teaches a method of therapeutically treating Alzheimer's disease (see explanation above for claim 1). Warne does not teach further monitoring the patient by at least one type of assessment selected from the recited assessments. Schenk teaches the use of the Mini-Mental State Exam (MMSE) to monitor Alzheimer's disease patients during therapeutic treatment with an antibody to A-beta (para [0008], [0408]-[0409]). It would have been obvious to use the MMSE to monitor the patients being treated using the method taught by Warne, because one of skill in the art would have known that the MMSE is routinely used to monitor Alzheimer's disease patients during therapy, including therapy with an A-beta antibody as taught by Schenk.

As to claim 19, Schenk teaches that the assessment type is an Alzheimer's Disease Assessment Scale (ADAS) (para [0408]). Although Schenk does not teach that the assessment type is the ADAS-cognitive (ADAS-COG), it would have been obvious to one of skill in the antito perform well-known subtypes of known assessments, including ADAS-COG, as such subtypes were routinely used to monitor Alzheimer's disease.

As to claims 20 and 24,	Schenk teaches that the	monitoring is adminis	itered on multi	płe occasions (pa	ıra (0409)).
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(Continu	ed in Supplemental Box)				
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In case the space in any of the preceding boxes is not sufficient.

Box V.2. Citations and Explanations (first Supplemental Box):

As to claim 25, Schenk teaches that the MMSE is performed before administering the dosage and 6 months after administering the dosage (pare [0409]), but does not teach that the MMSE is administered at week 4, week 16, or 1 year after administering the dosage. However, Schenk teaches that the monitoring is performed at least every six months (pare (0409)), which implies that the monitoring is probably performed 1 year after administering the dosage (i.e., after two iterations of 6 months). It further would have been obvious that the monitoring could be performed more often ("at least" ever six months implies it may be done with higher frequency), and one of skill in the ant would have determined that week 4 and week 16 were desirable times to monitor via routine experimentation.

As to claim 26, Schenk does not teach that the MMSE score measured after administration is higher than a previously assessed MMSE score. However, it would have been obvious to one of skill in the art that achieving a higher score would be a desirable result of therapeutic treatment.

Claims 3-4, 27, 29-31, 33-34, 41-42, and 45-56, lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of the article entitled "A case of reversible posterior leucoencephalopathy syndrome after rituximab infusion" by Mavragani et al. (hereinafter "Mavragani"), and further in view of the article entitled "Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIR; regimen for metastatic colon cancer" by Allen et al. (hereinafter "Allen").

As to claim 3, Warne teaches a method of therapeutically treating Alzheimer's disease (para [0036], [0050]), comprising administering by intravenous infusion to a patient suffering from the disease (para [0036], [0098]) a dosage of an antibody that specifically binds to an N-terminal fragment of beta amyloid peptide (A-beta) with a binding affinity of at least 10e7 M-1 (para [0059], [0127]). Warne does not teach monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema. Mavragani teaches that PRES (also referred to as "reversible posterior teukoencephalopathy syndrome" or "RPLS") is a side effect of administration of the monoclonal antibody rituximab (pg 1450, para 1, 6, 8). Alien teaches that PRES (RPLS) is a side effect of administration of the monoclonal antibody bevacizumab (abstract). Both Mavragani (pg 1451, para 3) and Alien (pg 1477, para 3) speculate that the RPLS is related to the antigen-binding specificity of the respective antibodies. However, one of skill in the art would have recognized that the same side effect in two different antibodies might be due to a generic side effect associated with administration of monoclonal antibodies regardless of binding specificity. Accordingly, it would have been obvious to one of skill in the art that PRES might be a potential side effect of administration of an antibody to A-beta, and it would have been obvious to monitor the patent for PRES, because it was routine in the art to monitor patents receiving medical treatment for expected side effects.

As to claim 4, Warne teaches a method of therapeutically treating Alzheimer's disease (para [0036], [0050]), comprising administering by intravenous infusion to a patient suffering from the disease (para [0036], [0098]) a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg (para [0035]), wherein the antibody specifically binds to an N-terminal fragment of beta amyloid peptide (A-beta) with a binding affinity of at least 10e7 M-1 (para [0059], [0127]). Warne does not teach monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema. However, it would have been obvious to one of skill in the art to do so, for the same reasoning given above for claim 3.

As to claim 27, Mayragani teaches that the monitoring comprises performing an MRI scan (pg 1450, para 6).

As to claims 29-30, Mavragani teaches that the monitoring comprises identifying at least one clinical symptom associated with PRES, such as headache, visual abnormalities, and seizures (pg 1451, para 1).

As to claims 31, 33, and 41 Mayragani does not teach reducing or suspending the dosage based on an outcome of the MRI scan that is indicative of PRES or vascular edema, or the identification of at least one clinical symptom associated with PRES or vascular edema. However, it would have been obvious to one of skill in the art to do so, because it was routine in the art to reduce or suspend a therapeutic treatment upon the manifestation of adverse side effects.

As to claim 34, Mavragani does not teach that the MRI scan is every 3 months, every 6 months, or every year. However, it would have been obvious to one of skill in the art to perform the monitoring at such intervals in order to monitor the progress of the treatment over time, and one of skill in the art would have determined the appropriate intervals at which to perform the MRI scan via routine experimentation.

As to claim 42, Mawagani teaches that the at least one clinical symptom associated with PRES is headache, visual abnormalities, or seizures (pg 1451, para 1).

(Continued in Supplemental Box)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Sox

in case the space in any of the preceding boxes is not sufficient. Continuation of:

Box V.2. Citations and Explanations (second Supplemental Box):

As to claims 45-46, Mavragani does not teach that the monitoring indicates presence of PRES or vascular edema at a first time point after administration, and absence of PRES or vascular edema at a second time point after the first time point, and the patient is administered a first dosage before the monitoring indicates presence of PRES or vascular edema, a second dosage or no dosage after the monitoring detects presence of PRES or vascular edema, and a third dosage after the monitoring detects absence of PRES or vascular edema, wherein the first and third dosage are higher than the second dosage. However, such a scenario would have been obvious to one of skill in the art, because it was routine in the art to reduce the dosage after the manifestation of an adverse side effect (i.e., after the first dosage), and then to increase it again (e.g., the the same dosage as the first dosage) in a subsequent dosage in order to determine whether the initial manifestation of the side effect was reat or an artifact.

As to claims 47-49, Warne teaches that the antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under PTA-5130 (para [0010], [0129]). Although Warne does not expressly teach that the antibody is bapineuzumab, the antibody produced by they hybridoma PTA-5130 is inherently bapineuzumab.

As to claim 50 and 53, Mavragani teaches that the PRES is determined using an MRI scan (pg 1450, para 6), but does not teach that the antibody is administered at a first dosage before PRES or vascular edema is determined from the MRI scan and a second dosage after PRES or vascular edema is determined from the MRI scan, and the second dosage is less than the first dosage. However, it would have been obvious to one of skill in the art to to administer the antibody (e.g., bapineuzumab) as recited, because it was routine in the art to reduce the dosage of a therapeutic agent after the manifestation of an adverse side effect.

As to ctaims 51-52 and 54-55, Warne teaches that the preferred dosage of the antibody such as bapineuzumab may be 3-5 mg/kg or 0.5-3 mg/kg (para (9035)). Although Warne does not teach a preferred first and second dosage, including wherein the second dosage is half of the first dosage, methods for determining the appropriate dosage were routine in the art, and one of skill in the art would have arrived at the appropriate dosage via routine experimentation.

As to claim 56, Warne teaches a kit for the treatment of Alzheimer's (para [0033]), comprising:

- (a) a glass vial (para [0035]) containing a formulation comprising:
 (i) about 10-250 mg of a humanized anti-A-bets antibody (para [0035]),
 (ii) about 4% mannitol or about 150 mM NaCl (para [0035]),
 (iii) about 5-10 mM histidine (para [0035]), and

 - (iv) about 10 mil methionine (para (0035)); and
- (b) instructions for use (para (0033)).

Warne does not teach that the instructions are to monitor a patient to whom the formulation is administered for PRES or vascular edema. However, it would have been obvious to one of skill in the art to monitor the patient for PRES, for the same reasoning given above for claims 3-4, and it therefore would have been obvious to one of skill in the art to include instructions for monitoring for PRES, because it was routine in the art to include instructions with kits relating to the use of their components and any adverse side effects that might be produced.

Claims 21-22 tack an inventive step under PCT Article 33(3) as being obvious over Warne in view of Schenk, and further in view of US 20060234912 A1 to Wang et al. (hereinafter "Wang").

As to claims 21, Warne in view of Schenk teaches a method of therapeutically treating Alzheimer's disease (see explanation above for claim 18). Neither Warne nor Schenk teaches that the assessment type is a Neurological Test Battery (NTB). Wang teaches the use of an NTB to monitor sensory and motor function (para [0159]). It would have been obvious to one of skill in the art to use an NTB to monitor an Alzheimer's disease treatment, because Wang teaches that the NTP is "standard" for monitoring sensory and motor function (para [0159]), and it would have been obvious that sensory and motor function may be affected in a neurological disorder such as Alzheimer's disease and should be monitored to determine the efficacy of treatment.

As to claim 22, Schenk teaches that the monitoring is administered on multiple occasions (para [0409]).

Claims 28, 32, 35, and 43-44 lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of Mavragani, further in view of Allen, and further in view of US 2006/0182321 A1 to Hu et al. (hereinafter "Hu").

As to claim 28, Warne in view of Mavrageni and Allen teaches a method of therapeutically treating Alzheimer's disease (see explanation

including a FLAIR sequence imaging, could provide a method for monitoring an Alzheimer's patient di	uring therapeutic treatment.
(Continued in Supplemental Box)	

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Box V.2. Citations and Explanations (third Supplemental Box):

As to claim 32, Wang does not teach reducing or suspending the dosage based on an outcome of the FLAIR sequence imaging that is indicative of PRES or vascular edema. However, it would have been obvious to one of skill in the art to do so, because it was routine in the art to reduce or suspend a therapeutic treatment upon the manifestation of adverse side effects.

As to claim 35, Wang does not teach that the FLAIR sequence imaging is every 3 months, every 6 months, or every year. However, it would have been obvious to one of skill in the art to perform the monitoring at such intervals in order to monitor the progress of the treatment over time, and one of skill in the art would have determined the appropriate intervals at which to perform the MRI scan via routine experimentation.

As to claims 43-44, Mavragani teaches that the monitoring comprises identifying at least one clinical symptom associated with PRES, such as headache, visual abnormalities, and seizures (pg 1451, para 1), but does not teach reducing or suspending the dosage based on an outcome of the FLAIR sequence imaging that is indicative of PRES or vascular edema and identification of at least one clinical symptom associated with PRES or vascular edema. However, it would have been obvious to one of skill in the art to do so, because it was routine in the art to reduce or suspend a therapeutic treatment upon the manifestation of adverse skile effects.

Claims 1-7, 9, 18-35, 41-163 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

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